UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/142,613	04/19/99	ISHIGURO K	1416/0P551PC

HM22/0509

WENDEROTH LIND & PONACK
2033 K STREET NW SUITE 800
WASHINGTON DC 20006

EXAMINER	
TURNER, S	
ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/142,613	Ishiguro
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on 2-26-01

2a) [X] This action is FINAL. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) 1 and 6-17 is/are pending in the applica

4a) Of the above, claim(s) 1 and 6-17 is/are withdrawn from considera

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) 1 and 6-17 is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirem

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [X] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [X] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [ ] Notice of References Cited (PTO-892)

16) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) [ ] Interview Summary (PTO-413) Paper No(s). _____

19) [ ] Notice of Informal Patent Application (PTO-152)

20) [ ] Other:

Response to Amendment

1. The amendment filed 2-26-01 has been entered into the record and has been fully considered.

2. Claims 2-5 are canceled. Claims 1, and 6-17 are pending.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Election/Restriction

4. Applicant's election of Group I, claims 1-6, species at phosphorylation site 199 and SEQ ID NO:2 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. The examiner notes that the original restriction was set forth under 35 USC 121, US restriction practice instead of 35 USC 372 for applications filed under 35 USC 371. The examiner notes that the group accordingly includes claim 7. The species election remains as previously set forth. The claims should be amended to the elected species.

New Rejections Based on Amendment

6. Newly submitted claims 1 and 6-17 are directed to inventions that appears to be independent or distinct from the invention originally claimed for the following reasons: The amended claims are so un-interpretable as set forth in the 35 USC 112, second paragraph

rejection below that the examiner cannot discern the peptide immunogen used or antibody obtained therefrom. Applicants are reminded of the species election to SEQ ID NO:2 and phosphorylation site 199 original scope of claim 1. Applicants are required to identify the amended claims which are readable on the elected species. The claims now appear to be additionally drawn to SEQ ID NO:1, to alternative sequences and to phosphorylation sites which were not elected. As these additional searches were not required for the rejection of the originally elected invention, they have not been performed and the claims as interpretable to alternative inventions and species are withdrawn as being directed to nonelected subject matter.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1 and 6-17 as reading on nonelected species are withdrawn from consideration as being directed to non-elected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 6-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses an antibody obtained by using as an immunogen a partial peptide comprising phosphorylation sites of phosphorylated tau protein in a paired helical filament. The specification provides for SEQ ID NOs:1-22. These SEQ ID NO's provide written description for those peptide species. However, the claims appear to be directed to alternative sequences, partial sequences and to phosphorylation sites which lack defined structure and thus encompass sequences which lack written description support under 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of the sequences defined as SEQ ID NO's:1-22 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. In addition clear identification of the phosphorylated residues is required to fully describe the phosphorylated sequences. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino

acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO's:1-22, but not the full breadth of claims meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1 and 6-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims have been amended to recite "two amino acid residues" and "plural amino acid residues" which are to be located "before and/or after the phosphorylation sites of amino acid sequence of SEQ ID NO:1....". The claims are so un-interpretable as to preclude meaningful examination. It is unclear what immunogens/residues applicants are intending to site and their various locations. Applicants are reminded that all

sequences are required to be encompassed by a representative SEQ ID NO. The skilled artisan cannot discern the peptide immunogens referred to and thus the examiner has been unable to evaluate the claims with respect to enablement. The metes and bounds, structural and functional requirements of the recited antibody are not discernable. Clarification is required.

11. Claims 1 and 6-17 recite the limitation "the phosphorylation sites" in the parent claim. There is insufficient antecedent basis for this limitation in the claim.

12. Claims 1 and 6-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: those amino acids and phosphorylation sites which represent the immunogen.

Claim Rejections - 35 USC § 102 or 103

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1 and 6-17 as they are readable on the elected species SEQ ID NO:2, phosphorylation site 199 are rejected under 35 U.S.C. 102(b) as being anticipated by IDS Reference Vandermeeren et al., J. of Neurochemistry 61:1828-34, 1993.

Vandermeeren teach detection of tau proteins in normal and Alzheimer's Disease CSF with a sensitive sandwich ELISA, see in particular title. The sandwich assay utilizes monoclonal antibody AT8 which recognizes abnormally phosphorylated serines 199-202 in tau. The antibody recognizes partial peptide sequences of SEQ ID NO:1. Thus, the reference teachings anticipate the claimed invention.

Applicants argue that Vandermeeren et al., fail to teach or suggest the antibody specificity and partial peptides of the present claims. In particular as newly directed to SEQ ID NO:1, and phosphorylated residues 231, 235, 412 and 413. Applicant further argue that although Vandermeeren discloses recognition of serines 199-202 the antibodies actually recognize serine at 202 and 205. Applicants point out that the if AT8 detects PHF-tau its concentration is probably below 3pg/ml and that AT120 reacts with CFS samples from patients other than Alzheimer's Disease and thus is not specific to Alzheimer's Disease like those exemplified by the specification. Applicants argue that Goedert negates the references teachings with respect to Serine 199.

Applicants arguments filed 2-26-01 have been fully considered but are not persuasive. Vandermeeren et al., teach a PHF-tau peptide which recognizes phosphorylated residues 199-202. Applicants claim amendments appear to have changed the invention to antibodies reactive to the full length tau peptide and which recognize alternative phosphorylation sites, such matter being nonelected subject matter, however which peptides appear to fall within the scope of the elected invention as the antibodies appear to recognize the elected epitope of phosphorylated

serine at position 199 of tau, as originally elected and claimed. The process limitation of applicants claims is only distinguishing where it results in the product claimed. The claimed product itself must be distinguishable from the product of the prior art. In instant case, the prior art antibody is not distinguishable from applicants invention as the elected phosphorylation sites are recognized via the antibody. The antibodies also appear to recognize a partial peptide epitope which is alternatively generated from either partial or full length peptides. The antibodies themselves are not distinguishable from the prior art as it is not clear the immunogen used to generate it nor the specificity to which it reacts. As to applicants arguments with respect to immunoreactivity with Alzheimer's patients samples, such does not appear to be a distinguishable feature between the antibodies. The Vandermeeren antibodies have been used in an assay for such screening of CSF from Alzheimer's patients. In addition it is noted that some of applicants antibodies as exemplified in the specification and figures 2-3 for example indicate immunoreactive epitopes which are shared in Alzheimer's and Normal patients, see in particular Figures 2-3. With regard to Goedert et al., as argued by applicants the reference teachings are insufficient to negate the teachings with respect to residue 199. In contrast, Goedert merely appears to suggest another recognized phosphorylation site. Thus, the rejection is maintained as the antibodies themselves are not distinguished from the prior art.

15. Claims 1 and 6-17 as they are readable on the elected species SEQ ID NO:2, phosphorylation site 199 are rejected under 35 U.S.C. 102(b) as being anticipated by IDS Reference Kimura et al., Dementia, 7:177-81, 1996.

Kimura et al., teach sequential changes of tau site specific phosphorylation during development of paired helical filaments, see in particular title. Kimura et al., teach generation of polyclonal antibody Anti-PP1 in particular which recognizes phosphoserine 199 and 202, see in particular Materials and Methods, p. 178, column 1, lines 23-25. In addition, Kimura teach analysis of immunoreactivity in Nondemented and Alzheimer's Disease Brains, see in particular pp. 178, column 2-p. 180, column 1 and Table 1. Tau comprises partial peptide sequences of SEQ ID NO:1. Thus, the reference teachings anticipate the claimed invention.

Applicants argue that the priority document of March 13, 1996 obviates the rejection.

Applicants arguments filed 2-26-01 have been fully considered but are not persuasive with respect to applicants claims as the claims appear broader than the specifications embodiments as disclosed in the priority document. Figures 5-6 and the data contained therein do not appear to be supported by the priority document.

16. Claims 1 and 6-17 as they are readable on the elected species SEQ ID NO:2, phosphorylation site 199 are rejected under 35 U.S.C. 102(b) as being anticipated by IDS Reference Yamaguchi et al., Acta Neuropathol., 92:232-241, 1996 and Takahashi et al., J of Neurochemistry, 64:1759-68, April 1995.

Yamaguchi et al., teach antiserum PS199 directed to the phosphorylated synthetic peptide of tau 195-205 which recognizes phosphorylated Ser199 of tau and the detection of neurofibrillary tangles in control, Alzheimers Disease and Down Syndrome brains, see in

particular p. 233, column 1, lines 37-39 and Figures 2-6. Thus the reference teachings anticipate the claimed invention.

Takahashi et al., also teach antiserum PS199 antibodies directed to phosphorylated Serine199 and analysis of immunoreactivity in rat brain, see in particular title, abstract.

Applicants argue that the priority document of March 13, 1996 obviates the rejection. In addition, with respect to Takahashi, applicants argue that the invention as amended is not directed to position 199 or 396.

Applicants arguments filed 2-26-01 have been fully considered but are not persuasive with respect to applicants claims as the claims appear broader than the specifications embodiments as disclosed in the priority document. Figures 5-6 and the data contained therein do not appear to be supported by the priority document. In addition Takahashi, as set forth was published April 1995 and thus is prior art regardless of the priority date. With respect to Takahasi, the elected invention and that searched was phosphorylation site 199. As such the prior art reference reads on the elected invention. As the claims can be construed to remain partially drawn to the peptides of Takahashi the rejection is maintained.

17. Claims 1 and 6-17 as they are readable on the elected species SEQ ID NO:2, phosphorylation site 199 are rejected under 35 U.S.C. 102(b) as being anticipated by Biernat et al., EMBO J., 11(4):1593-97, 1992.

Biernat et al., teach that the switch of tau protein to an Alzheimer-like state includes the

phosphorylation of two serine-proline motifs upstream of the microtubule binding region using monoclonal antibody AT8 which recognizes the phosphorylation of serines 199 and/or 202, see in particular title, abstract. Biernat includes analysis of AD brain, see in particular Figure 7. Thus, the reference teachings anticipate the claimed invention.

Applicants argue that Biernat teaches an antibody obtained by using the whole phosphorylated tau protein as immunogen and that Biernat et al do not teach the switch of tau protein to an Alzheimer-like state includes phosphorylation of serine motifs upstream of the microtubule binding region and does not teach detection of Alzheimers by examining reactivity using antibodies having as an immunogen a partial peptide containing a phosphorylated site in tau PHF. Applicants argue that Goedert negates the references teachings with respect to Serine 199.

Applicants arguments filed 2-26-01 have been fully considered but are not persuasive. With regard to Goedert et al., as argued by applicants the reference teachings are insufficient to negate the teachings with respect to residue 199. In contrast, Goedert merely appears to suggest another recognized phosphorylation site. As to the method of detection, the examiner notes that the reference teaches examination of immunoreactivity with the claimed antibody. As the antibody reacts with the peptide it appears to detect a patient suspected of having Alzheimer's. Alternatively, the examiner notes that the detection of such immunoreactivity does not provide for the identification of Alzheimer's Disease. The method steps are met by the reference.

Status of Claims

18. No claims are allowed.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

20. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
May 7, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud